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RESULTS OF IMPORT SUBSTITUTION ANALYSIS OF ANTI-CANCER MEDICATIONS IN THE RUSSIAN FEDERATION (2013–2018)

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The aim. *Due to the social importance of anticancer drugs, the aim of the study is to conduct a comparative analysis of the range of domestic and foreign anticancer medications included in the Lists of Vital and Essential Drugs in 2013 and 2018 in the aspect of import substitution.*
Materials and methods. *The study was conducted by comparing the data on the registered anticancer preparations included in the list of Vital and Essential Drugs in the State Register of Medicines in 2013 and 2018. Statistical processing of the data was carried out on the basis of Fisher Z-test method.*
Results. *All in all, there were 286 trade names of anticancer drugs registered in the Russian Federation in 2013. 94 of them, i.e. 33%, were Russian-made. In 2013, there were 19 pharmaceutical substances of domestic production in the analyzed group, which accounted for 27% of 71 INNs (International nonproprietary name). As for 71 INNs, in 2018 there were 393 registered trade names of anticancer drugs. 162 drugs, i.e. 41%, were Russian-made. From 2013 to 2018, a statistically significant positive trend of the increase in the number of domestic anticancer drugs by 8%. was revealed.*
Conclusion. *In order to increase the volume of import substitution in the production of anticancer drugs, it is necessary to provide state support to Russian manufacturers, who register domestic analogues for the first time. A particular attention should be paid to the production of domestic pharmaceutical substances, without which it is impossible to ensure the drug safety of the country.*
Keywords: *drugs, medicines, the State Register of Medicines, import substitution, pharmaceutical substances, anticancer drugs*

РЕЗУЛЬТАТЫ АНАЛИЗА ИМПОРТОЗАМЕЩЕНИЯ ПРОТИВООПУХОЛЕВЫХ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ В РОССИЙСКОЙ ФЕДЕРАЦИИ ЗА 2013–2018 ГОДЫ

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Цель. *В виду социальной значимости противоопухолевых лекарственных препаратов (ЛП) цель исследования – провести сравнительный анализ ассортимента отечественных и зарубежных противоопухолевых ЛП, входящих в перечни жизненно необходимых и важнейших лекарственных препаратов (ЖНВЛП) в 2013 и 2018 гг. в аспекте импортозамещения.*
Материалы и методы. *Исследование проведено сравнением данных о зарегистрированных противоопухолевых препаратах, входящих в перечни ЖНВЛП в 2013 и 2018 гг. в Государственном реестре лекарственных средств. Статистическая обработка полученных данных была проведена методом z-критерия Фишера.*

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Результаты. *Всего в РФ на 2013 год было зарегистрировано 286 торговых наименований противоопухолевых ЛП, из них российского производства 94 препарата, т.е. 33%. Фармацевтических субстанций отечественного производства в анализируемой группе в 2013 году было 19, что составляло 27% от 71 МНН (Международное непатентованное наименование). В 2018 году по 71 МНН зарегистрировано 393 торговых наименования противоопухолевых ЛП, из них российского производства – 162 препарата, т.е. 41%. Выявлена статистически значимая положительная тенденция увеличения количества противоопухолевых препаратов отечественного производства с 2013 года по 2018 – на 8%.*
Заключение. *В целях увеличения объема импортозамещения при производстве противоопухолевых ЛП необходимо обеспечить государственную поддержку российских производителей, впервые регистрирующих отечественные аналоги. Особое внимание следует уделить производству отечественных фармацевтических субстанций, без которых невозможно обеспечить лекарственную безопасность страны.*
Ключевые слова: *лекарственные средства, лекарственные препараты, импортозамещение, фармацевтические субстанции, противоопухолевые лекарственные препараты*

INTRODUCTION

Ensuring the health of the nation is determined by the state national policy in the field of health care including drug provision of the population.

The organization of the production of domestic drugs is the aim of the state policy in the sphere of providing the population with vital and essential drugs, the production of which is planned to be raised to 90% in the Russian Federation by 2025 [1–4].

Cancer is considered to be one of the important problems of modern health care. It is one of the most common pathologies after insult and myocardial ischemia. And every year the number of cancer patients is growing steadily.

In 2016, 599 thousand cases of malignant neoplasms were detected in the Russian Federation for the first time. Mortality rate due to neoplasms was 201.6 per 100 thousand population. At the end of 2016, more than 3 million patients were registered in territorial oncological institutions [5].

MATERIALS AND METHODS

Due to the social importance of treating cancer patients, a comparative analysis of the range of domestic and foreign anticancer drugs included in the lists of Vital and Essential Drugs (VED) in 2013 and 2018 in the aspect of import substitution, has been carried out [6, 7]. The list of Vital and Essential Drugs dated 2013, was taken as a starting point due to the fact that in 2013 Strategy of Drug Provision of the Population of the Russian Federation was adopted.

According to the DSM Group data, in 2013, about 90 billion rubles were spent on all anticancer drugs from all sources of financing including individuals, and 95 million packages were purchased [8].

At the end of 2017, about 123 billion rubles were spent on anticancer drugs and 80 million packages were purchased [9]. Thus, there is an increase in the cost value for anticancer drugs – by 4% over 4 years and a decrease in the natural consumption of this group by 15%.

The scientific research was performed sequentially and included three interrelated stages.

The objective of the first stage of the study was to compare the lists of Vital and Essential Drugs adopted in 2013 and 2018. 71 INNs of the drugs coincide in the lists of the VED in 2013 and 2018. The group of anticancer drugs included in the list of VED in 2018 is 65 INNs larger than in the list of VED in 2013.

The task of the second stage of the study was a comparative analysis of the range of the drugs registered in the Russian Federation and the substances for their production, hereby, 71 INNs were included in the both lists (Table 1). In the analysis, the data from the State Register of Medicines were used.

Table 1. Medicines for treating patients with oncological diseases in Vital and Essential Drugs lists (2013–2018)

№	INN	Registered by trade names (assortment positions)				The number of registered Russian substances (assortment positions)	
		Russian manufacturers		Foreign manufacturers			
		2013	2018	2013	2018	2013	2018
1	Cyclophosphamide	4	4	1	1	1	1
2	Carmustine	–	–	2	2		–
3	Ifosfamide	3	3	1	1	1	1
4	Melphalan	–	–	2	2	–	
5	Chlorambucil	–	–	2	2	–	–
6	Temozolomide	3	9	7	4	–	2
7	Methotrexate	3	5	3	4	–	–
8	Pemetrexed	–	2	1	1	–	1
9	Raltitrexed	–	–	2	2	–	–

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Continuation of table 1

№	INN	Registered by trade names (assortment positions)				The number of registered Russian substances (assortment positions)	
		Russian manufacturers		Foreign manufacturers			
		2013	2018	2013	2018	2013	2018
10	Nelarabine	–	–	2	2	–	–
11	Gemcitabine	6	5	10	10	1	1
12	Fludarabine	1	6	3	8	1	1
13	Capecitabine	2	7	4	4	–	3
14	Fluorouracil	2	5	4	3	–	–
15	Cytarabine	1	2	3	5	–	–
16	Vinblastine	1	2	2	3	–	–
17	Vincristines	1	3	1	2	–	–
18	Vinorelbine	4	2	4	6	–	–
19	Etoposide	1	1	5	5	–	–
20	Docetaxel	4	3	4	6	–	1
21	Paclitaxel	3	3	12	12	–	–
22	Bevacizumab	–	1	2	1	–	1
23	Trastuzumab	–	1	2	1	–	1
24	Cetuximab	–	–	1	1	–	–
25	Gefitinib	–	2	1	1	–	1
26	Dasatinib	–	1	1	1	–	1
27	Imatinib	5	17	4	10	1	5
28	Sorafenib	–	1	1	1	–	1
29	Sunitinib	–	1	1	1	–	1
30	Asparaginase	1	2	1	1	–	–
31	Bortezomib	1	5	1	1	–	3
32	Irinotecan	3	3	10	10	–	1
33	Medroxyprogesterone	1	1	5	5	–	–
34	Leuprorelin	–	–	3	3	–	–
35	Triptorelin	–	1	1	2	–	1
36	Tamoxifen.	4	4	7	7	–	–
37	Fulvestrant	–	–	1	1	–	–
38	Bicalutamide	7	8	7	6	–	3
39	Flutamide	3	3	4	8	–	–
40	Anastrozole	3	5	7	6	–	1
41	Filgrastim	6	7	7	8	–	4
42	Interferongamma	1	1	-	-	1	1
43	Anoxemiabromide	1	1	-	-	1	1
44	Vaccine for treatment of bladder cancer BCG	1	1	-	-	1	1
45	Glatirameracetate	1	3	1	1	–	1
46	Glutamyl-cysteinyl-glycinedisodium	1	1	-	-	1	1
47	Megluminacridonacetate	1	1	-	-	1	1
48	Tiloron	4	7	3	3	4	4
49	Abatacept	–	–	1	1	–	–
50	Mycophenolatemofetil	2	2	4	6	–	2
51	Mycophenolicacid	–	–	1	1	–	–
52	Everolimus	–	–	1	1	–	–
53	Infliximab	1	1	3	3	–	–
54	Etanercept	–	–	1	1	–	–
55	Basiliximab	–	–	1	1	–	–
56	Tocilizumab	–	–	1	1	–	–
57	Tacrolimus.	–	6	2	12	–	–
58	Cyclosporine	–	–	6	6	–	–

Continuation of table 1

№	INN	Registered by trade names (assortment positions)				The number of registered Russian substances (assortment positions)	
		Russian manufacturers		Foreign manufacturers			
		2013	2018	2013	2018	2013	2018
59	Azathioprine	1	1	1	1	1	1
60	Lenalidomide	–	2	1	2	–	2
61	Interferon alpha-2b	5	5	3	3	4	4
62	Busulfan	–	–	2	2	–	–
63	Hydroxycarbamide	–	3	3	6	–	1
64	Goserelin	–	–	1	1	–	–
65	Ibandronicacid	–	–	2	2	–	–
66	Interferon alpha-2a	–	–	1	1	–	–
67	Lomustine	–	–	1	1	–	–
68	Mercaptopurine	–	1	3	3	–	1
69	Nilotinib	–	–	1	2	–	1
70	Rituximab	1	1	1	1	–	1
71	Tretinoin	–	–	3	3	–	–

RESULTS AND DISCUSSION

In total, in the Russian Federation 286 trade names of anticancer drugs were registered in 2013. 94 of them, i.e. 33%, were Russian-made. In 2013, in the analyzed group there were 19 pharmaceutical substances of domestic production which accounted for 27% of 71 INNs.

In 2018, 71 INNs were registered under 393 trade names of anticancer drugs, 162 of which, i.e. 41%, were Russian-made. Thus, there is an 8% increase in the share of domestic drugs in the anticancer group.

In 2018, 37 pharmaceutical substances of domestic production were registered in the analyzed group. That accounted for 51% of the 71 INNs.

Compared with 2013, 11 INNs of Russian production appeared additionally in 2018.

To confirm the reliability of the results obtained, statistical processing on the basis of the Fisher z-test method was performed.

The use of the program for comparing the indicators of the two groups on the Z-criterion, was the most acceptable for the purposes of our study. The Z-criterion is one of non-parametric criteria. The data of $Z = 4.54$ ($p = 0.0001$) shows statistically significant differences in the group of anticancer drugs included in the List of Vital and Essential Drugs made in Russia in 2013 and 2018.

As for 33 INNs, the number of domestic and foreign manufacturers of medicines have not changed.

In 2018, pharmaceutical substances were produced by 37 domestic enterprises, i.e. 51% more than in 2013. But at the same time a certain tendency was revealed. It was connected with the fact that the same medications began to be produced by several manufacturers simultaneously. Thus, there were 43 trade names, i.e. about 26% out of 162 registered domestically manufactured medications which referred to 5 MNNs (Imatinib, Temozolomide, Tacrolimus, Fludarabine and Bortezomib). The question arises why domestic manufacturers have chosen those INNs and how the number of the registered drugs is related to the real need for anticancer drugs.

The approaches to the registration of the 5 domestic and foreign drugs given above in the lists of INN, are not clear. It would be logical if an increase in the number of the registered drugs of domestic production should be accompanied by a decrease in the number of imported anticancer drugs registered in the Russian Federation.

However, this ratio is observed only for Temozolomide and Bortezomib. In 2013–2018 the number of Russian manufacturers of Temozolomide increased from 3 to 9, and the number of foreign manufacturers decreased from 7 to 4. From 2013 to 2018, the number of Russian manufacturers of Bortezomib increased from 1 to 5, but the number of foreign manufacturers has not changed.

As for the remaining 3 medications, there is a tendency of a parallel increase in the number of registered domestic and foreign drugs.

In particular: from 2013 to 2018, the number of Russian manufacturers of Imatinib increased from 5 to 17, and the number of medications of foreign manufacturers increased from 4 to 10. During this period, the number of Russian manufacturers of Fludarabinaz increased from 1 to 6, and the number of drugs of foreign manufacturers increased from 3 to 8.

The situation with Tacrolimus is similar: in 2018 6 Russian manufacturers were registered (in 2013 there was none), and the number of foreign manufacturers increased by 8 (from 2 to 10).

At the third stage, 65 INNs have been analyzed. They make up a group of anticancer drugs, first included in the list of VED in 2018 (Table 2).

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Table 2. Medicines for treating patients with oncological diseases in Vital and Essential Drugs lists (2018)

№	INN	Registered by trade names (assortment positions)		The number of Registered Russian substances (assortment positions)
		Russian manufacturers	Foreign manufacturers	
1	Bendamustine	–	1	–
2	Dacarbazine	2	2	–
3	Azacitidine	–	1	–
4	Daunorubicin	3	–	2
5	Doxorubicin	7	4	1
6	Idarubicin	3	1	–
7	Mitoxantrone	4	2	–
8	Epirubicin	2	2	–
9	Bleomycin	4	2	1
10	Mitomycin	1	2	–
11	Carboplatin	3	6	2
12	Oxaliplatin	4	9	1
13	Cisplatin	4	3	–
14	Procarbazine	–	1	–
15	Brentuximabvedotin	–	1	–
16	Nivolumab	–	1	–
17	Obinutuzumab	–	1	–
18	Panitumumab	–	1	–
19	Pembrolizumab	1	1	–
20	Pertuzumab	–	1	–
21	TrastuzumabEltanin	–	1	–
22	Afatinib	–	1	–
23	Vandetanib	–	2	–
24	Dabrafenib	–	2	–
25	Ibrutinib	1	1	–
26	Krizotinib	–	1	–
27	Nintedanib	–	1	–
28	Pazopanib	–	2	–
29	Regorafenib	–	1	–
30	Rukolaine	–	1	–
31	Trametinib	–	2	–
32	Erlotinib	–	3	–
33	Aflibercept	–	2	–
34	Wiimotelib	–	1	–
35	Carfilzomib	–	1	–
36	Tumor necrosis factor alpha-1 (thymosin recombinant)	1	1	1
37	Eribulin.	–	1	–
38	Buserelin	2	–	2
39	Goserelin	–	1	–
40	Insulated	–	1	–
41	Abiraterone	3	2	3
42	Degarelix	–	1	–
43	Interferon beta-1a	1	2	1
44	Interferon beta-1b	2	1	1
45	Peginterferon alpha-2a	–	1	–
46	Peginterferon alpha-2b	2	1	1
47	Interferon beta-1a	–	1	–
48	Cepeginterferon alpha-2b	1	1	1
49	Alemtuzumab	–	2	–
50	Apremilast	–	1	–

Continuation of table 1

№	INN	Registered by trade names (assortment positions)		The number of Registered Russian substances (assortment positions)
		Russian manufacturers	Foreign manufacturers	
51	Vedolizumab	–	1	–
52	Leflunomide	4	2	–
53	Natalizumab	–	1	–
54	Teriflunomide	1	1	1
55	Tofacitinib	–	1	–
56	Fingolimod	–	1	–
57	Eculizumab	–	1	–
58	Adalimumab	–	1	–
59	Golimumab	–	1	–
60	Certolizumabpegol	–	1	–
61	Canakinumab	–	1	–
62	Secukinumab	–	1	–
63	Tocilizumab	–	1	–
64	Ustekinumab	–	1	–
65	Pirfenidone	–	1	–

As for 65 INNs, 153 trade names included in this group of drugs were registered in 2018. 56 of them, i.e. 35%, were made in Russia.

The especially alarming factor is that out of 65 INNs included in the list of VED in 2018, only 13 substances (20%) and 22 INNs are produced in Russia (34%), and 38 registered INNs are produced by only one foreign manufacturer.

Thus, the conducted study has shown that out of 136 INNs of anticancer drugs, which were included in the list of Vital and Essential Drugs in 2018, 546 trade names were registered: 218 drugs are Russian-made, which is 40% of all the registered anticancer drugs in the Russian Federation.

CONCLUSIONS

The study has shown a statistically significant positive though not high enough tendency to increase the number of anticancer drugs of domestic production from 2013 to 2018 – by 8%.

In order to optimize the import substitution of anticancer drugs, it is necessary to do the following.

1. Determine the real need of health care in the Russian Federation for the entire range of anticancer drugs.

2. Taking into account a high social significance of this group of medications, the possibility of forming a state order for their production and distributing it among domestic producers, providing them with state support, should be considered.

3. Limit the number of registered generics of anticancer drugs due to a more thorough assessment of their benefits.

4. Particular attention should be paid to the production of domestic pharmaceutical substances, without which it is impossible to ensure the drug safety of the country.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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